Complete Summary

GUIDELINE TITLE

American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism.

BIBLIOGRAPHIC SOURCE(S)

AACE Thyroid Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocr Pract 2002 Nov-Dec;8(6):457-69. [46 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Hyperthyroidism due to toxic diffuse goiter (Graves' disease), toxic adenoma, toxic multinodular goiter (Plummer´s disease), painful subacute thyroiditis, silent thyroiditis, including lymphocytic and postpartum variations, iodine-induced hyperthyroidism (e.g., related to amiodarone therapy), excessive pituitary thyroid-stimulating hormone (TSH) or trophoblastic disease, excessive ingestion of thyroid hormone
- Subclinical hyperthyroidism
- Primary hypothyroidism due to chronic autoimmune thyroiditis (Hashimoto's disease), surgical removal of the thyroid gland, thyroid gland ablation with radioactive iodine, external irradiation, a biosynthetic defect in iodine organification, replacement of the thyroid gland by tumor (lymphoma), and drugs such as lithium or interferon; secondary hypothyroidism due to pituitary and hypothalamic disease
- Subclinical hypothyroidism

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Endocrinology
Family Practice
Internal Medicine
Obstetrics and Gynecology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To present a framework for the diagnosis, treatment, and follow-up of patients with hyperthyroidism and hypothyroidism
- To address the difficulties involved in diagnosing thyroid disease and offer a system of care that should improve outcome and reduce costs

TARGET POPULATION

- Individuals with overt or subclinical hyperthyroidism
- Individuals with primary, secondary, or subclinical hypothyroidism

INTERVENTIONS AND PRACTICES CONSIDERED

Hyperthyroidism

Diagnosis

1. Comprehensive history and physical examination including: weight and blood pressure; pulse rate and cardiac rhythm; thyroid palpation and auscultation (to determine thyroid size, nodularity, and vascularity); neuromuscular examination; eye examination (to detect evidence of exophthalmos or ophthalmopathy); dermatologic examination; cardiovascular examination; lymphatic examination (nodes and spleen).
2. Laboratory evaluation including the sensitive thyroid-stimulating hormone (TSH) assay, measurement of serum thyroxine (T_4), triiodothyronine (T_3) radioimmunoassay, free T_3 and T_4 levels, measurement of thyroid autoantibodies, including TSH receptor antibodies of thyroid-stimulating immunoglobulins, radioactive iodine uptake, and thyroid scan
3. Orbital ultrasonography, computed tomography, magnetic resonance imaging, and serial exophthalmometry in patients with Graves´ ophthalmopathy
4. Local mechanical therapies (e.g., sunglasses, artificial tears) and corticosteroids or retro-orbital irradiation in patients with Graves´ ophthalmopathy

Treatment and Management

1. Radioactive iodine, antithyroid drugs (methimazole and propylthiouracil), or surgery (thyroidectomy) for patients with Graves' disease
2. Beta-adrenergic antagonist before radioiodine therapy
3. Follow-up examinations
4. Thyroid replacement therapy after achieving hypothyroid state
5. Special considerations in the pregnant patient
6. Patient education and involvement in care

Hypothyroidism

Diagnosis

1. Laboratory evaluation including sensitive TSH assays, free thyroxine estimate, measurement of thyroid autoantibodies, thyroid scan, and ultrasonography

Treatment and Management

1. Levothyroxine for the goiters of patients with chronic thyroiditis and for patients with subclinical hypothyroidism
2. Replacement therapy for patients with clinical hypothyroidism
3. Reassessment at frequent intervals, with measurement of serum TSH and free thyroxine estimates
4. Management considerations for hypothyroidism during pregnancy or for patients with concurrent conditions, such as diabetes mellitus, infertility, depression, euthyroid sick syndrome

MAJOR OUTCOMES CONSIDERED

- Morbidity due to subclinical hyperthyroidism, including accelerated rate of bone loss, cardiac hypertrophy, and atrial fibrillation
- Morbidity due to subclinical hypothyroidism, including alterations in lipid metabolism and abnormalities in cardiac, gastrointestinal, neuropsychiatric, and reproductive function
- Remission and relapse rates after treatment for hyperthyroidism
- Adverse effects of thyroid replacement therapy
- Sensitivity of thyroid-stimulating hormone (TSH) assays and other laboratory tests for diagnosing thyroid disease

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Fourteen physicians are acknowledged as reviewers in the guideline document.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Hyperthyroidism

Diagnosis

A comprehensive history and physical examination should be elicited, and a thorough physical examination should be performed, including the following.

- Weight and blood pressure
- Pulse rate and cardiac rhythm
- Thyroid palpation and auscultation (to determine thyroid size, nodularity, and vascularity)
- Neuromuscular examination
- Eye examination (to detect evidence of exophthalmos or ophthalmopathy)
- Dermatologic examination
- Cardiovascular examination
- Lymphatic examination (nodes and spleen)

Laboratory Evaluation

The development of sensitive thyroid-stimulating hormone (TSH) assays has considerably facilitated the diagnosis of hyperthyroidism. The sensitive TSH test refers to a TSH assay with a functional sensitivity of 0.02 or less. Hyperthyroidism of any cause (except excess TSH production) results in a lower-than-normal TSH level (suppressed TSH). The sensitive TSH assay is the single best screening test for hyperthyroidism, and in most outpatient clinical situations, the serum TSH is the most sensitive test for detecting mild (subclinical) thyroid hormone excess or deficiency.

In patients with unstable thyroid states, such as those recently treated for hyperthyroidism or those who have been receiving excess thyroid hormone replacement, serum thyroxine (T_4) measurement more accurately indicates the thyroid status than does serum TSH. Patients with chronic or recent severe hyperthyroidism or hypothyroidism will benefit from having both TSH and T_4 monitored for one year until their condition becomes stable. Elderly patients or those patients suspected of being noncompliant also should have both TSH and T_4 measurements monitored.

Other laboratory and isotope tests may include the following:

- T_4 or free T_4
- Triiodothyronine (T_3) radioimmunoassay (RIA) or free T_3. Abnormal results of T_4 or T_3 measurements are often due to binding protein abnormalities rather than abnormal thyroid function. Therefore, total T_4 or T_3 must be determined in conjunction with some measure of their thyroid hormone binding such as T_3 resin uptake or assay of thyroid-binding globulin to yield a "free thyroid hormone estimate." Commercial laboratories often call these methods free T_4 or free T_3 even though they do not measure free hormone directly.
- Thyroid autoantibodies, including TSH receptor antibodies (TRAb) or thyroid-stimulating immunoglobulins (TSI). These studies are not routinely necessary but may be helpful in selected cases, such as in patients with hyperthyroidism during pregnancy.
- Radioactive iodine uptake
- Thyroid scan with either Iodine 123 (^{123}I) (preferably) or technetium 99m (^{99m}Tc). Such a scan is not a thyroid function test but is done to help determine the cause of the hyperthyroidism. The scan may also be useful in

assessing the functional status of any palpable thyroid irregularities or nodules associated with a toxic goiter.
- Reverse T_3 testing is seldom, if ever, helpful in clinical practice.

Refer to the original guideline document for details about differential diagnosis.

Treatment and Management

Three types of therapy are available for Graves´ disease:

- surgical intervention
- antithyroid drugs
- radioactive iodine

Surgical Intervention

Although thyroidectomy for Graves' disease was frequently used in the past, it is now uncommonly performed in the United States unless coexistent thyroid cancer is suspected. Pregnant patients with hyperthyroidism who are intolerant of antithyroid drugs or nonpregnant patients desiring definitive therapy but who refuse radioactive iodine treatment are candidates for surgical intervention. Some physicians prefer surgical treatment of pediatric patients with Graves' disease or patients with very large or nodular goiters. Potential complications associated with surgical management of Graves' disease include hypoparathyroidism and vocal cord paralysis in a small proportion of patients. Surgeons trained and experienced in thyroid surgical procedures should perform this operation.

Antithyroid Drugs

Antithyroid drugs, methimazole and propylthiouracil, have been used since the 1940s and are prescribed in an attempt to achieve a remission. The remission rates are variable, and relapses are frequent. The patients in whom remission is most likely to be achieved are those with mild hyperthyroidism and small goiters. Antithyroid drug treatment is not without the risk of adverse reactions, including minor rashes and, in rare instances, agranulocytosis and hepatitis. The success of this therapy depends on a high degree of patient adherence to recommendations. Hyperthyroidism during pregnancy is one clear indication for antithyroid drug treatment. Elderly or cardiac patients may require "pretreatment" with antithyroid drugs, before radioiodine therapy. Moreover, some endocrinologists prefer antithyroid drug therapy in childhood Graves' disease. Treatment of Graves' disease with antithyroid drugs alone is an alternative therapeutic strategy but is used in only a minority of patients in the United States.

Radioactive Iodine

In the United States, radioactive iodine is currently the treatment of choice for Graves' disease. Many clinical endocrinologists prefer an ablative dose of radioactive iodine while some prefer a smaller dose that would attempt to render the patient euthyroid. Ablative therapy with radioactive iodine yields quicker resolution of the hyperthyroidism than does small-dose therapy and thereby minimizes potential hyperthyroid-related morbidity.

Radioactive iodine therapy is safe, but most treated patients become hypothyroid and require lifelong thyroid replacement therapy. Some clinical endocrinologists are hesitant to use radioactive iodine to treat patients of childbearing age, but no evidence has suggested that such therapy has any adverse effects. Specifically, studies have found no effect on fertility, no increased incidence of congenital malformations, and no increased risk of cancer in patients treated with radioactive iodine or in their offspring. Elderly or cardiac patients with Graves' disease may require treatment with antithyroid drugs prior to radioactive iodine, to deplete the gland of stored hormone and reduce the risk of excessive post-treatment hyperthyroidism secondary to Iodine 131 (^{131}I)-induced thyroiditis. Use of radioactive iodine is contraindicated during pregnancy because it may ablate the thyroid in the fetus. Before radioactive iodine treatment, a negative pregnancy test should be obtained in all women of childbearing age, and pregnancy should be postponed after such therapy. A waiting period of 6 months is frequently advised. Furthermore, radioactive iodine should not be given to women who are breast-feeding because it appears in the breast milk. The use of radioactive iodine in patients younger than 20 years has become commonplace.

After administration of a dose of radioactive iodine, thyroid replacement therapy should be carefully initiated during the time the patient's thyroid function passes through the normal range into the hypothyroid range. The final thyroid replacement dose must be individualized. This approach produces a prompt resolution of the hyperthyroidism with a minimum of hypothyroid morbidity.

System of Care

Once the diagnosis of Graves' disease with hyperthyroidism is established, the patient should be given a complete explanation of the illness and options for treatment. The goal is to involve the patient as a partner in the medical decision-making process and care, rather than have the endocrinologist dictate the choice of therapy.

Patients who elect to receive radioactive iodine should be given an explanation of the treatment, and a consent form for such therapy should be signed (refer to Appendix A in original guideline document for details). After receiving radioactive iodine, patients should be given an instruction sheet that itemizes appropriate precautions and explains follow-up management (refer to Appendix B in original guideline document for details).

The radioactive iodine uptake should be assessed prior to treatment to ensure that the uptake is adequate at the time of therapy, to rule out the presence of a variant of thyroiditis or iodine contamination, and to help determine the dose of radioactive iodine. A thyroid scan is also useful in distinguishing toxic nodular goiter and toxic adenoma from Graves' disease. Typically, toxic nodular goiter typically is more resistant to radioactive iodine and frequently requires a larger dose.

Beta-adrenergic antagonists provide symptomatic relief and can be administered before radioactive iodine is given. Because patients with hyperthyroidism may be relatively resistant to the effects of beta-adrenergic blocking agents, larger and more frequent doses may be necessary. The dose of these drugs can be tapered and discontinued once the patient is no longer hyperthyroid. In addition, in severe

thyrotoxic states, adjuvant treatment can include organic or inorganic iodides and antithyroid drugs following radioactive iodine therapy.

After treatment with radioactive iodine, patients should have follow-up examinations at frequent intervals (varying from 4 to 6 weeks, but individualized for each case) until they are euthyroid and their condition is stable. Most patients will require full thyroid hormone replacement therapy. Patients usually become hypothyroid within 3 months and could begin receiving partial replacement doses of levothyroxine approximately 2 months after receiving radioactive iodine. This schedule is determined by laboratory testing and clinical evaluation. At this time the patient´s thyroid status is quickly changing from euthyroid to hypothyroid. At this stage the TSH may not be a good indicator of function because it fails to rise quickly. From 2 weeks to several months may elapse before TSH responsiveness is recovered, and free thyroid hormone estimate tests are more accurate than TSH values during this interval.

When the condition of patients has stabilized, the frequency of visits and reevaluations can be extended. A common schedule for follow-up consultations is at 3 months, at 6 months, and then annually, but this can be modified on the basis of the physician´s judgment.

Hyperthyroidism During Pregnancy

Hyperthyroidism during pregnancy presents special concerns and is best managed collaboratively by an obstetrician and a clinical endocrinologist. Use of radioactive iodine is contraindicated in pregnancy because it crosses the placenta. Antithyroid drugs are the treatment of choice for hyperthyroidism during pregnancy and propylthiouracil is clearly preferred over methimazole. Antithyroid drugs also cross the placenta, and overtreatment with them may adversely affect the fetus. Therefore, the lowest possible dose of antithyroid drug should be used to keep the mother's thyroid function at the upper limit of normal. Because pregnancy itself has an ameliorative effect on Graves' disease, the dose of antithyroid drug required usually decreases as the pregnancy progresses. Often the antithyroid drug can be discontinued prior to delivery. If surgical treatment does become necessary, it is best done during the second trimester of pregnancy.

The patient's active participation in treatment is critical to the successful outcome of pregnancy in the presence of Graves' disease. Of importance, the patient must understand the risk of the disease, the pathophysiologic factors, and the mechanisms involved in therapy. Patient education will enhance adherence to recommended therapy as well as awareness of changes that may necessitate treatment alterations. With this background, the patient should become more aware of the problems that might occur and should alert her endocrinologist.

The patient should also be informed about changes that may occur in her health or her baby's health during the postpartum period. She should be advised to inform the pediatrician of her thyroid disease and of the possibility that neonatal hyperthyroidism or hypothyroidism might develop in the baby. The infant´s thyroid function must be tested at birth.

The patient should also be aware that postpartum recurrence of the hyperthyroidism is likely. This finding can be related to the Graves' disease or

postpartum thyroiditis. If overt hyperthyroidism due to Graves´ disease develops after delivery, the patient may be offered the alternative of resuming antithyroid drug therapy or receiving radioactive iodine.

Radioactive iodine therapy is contraindicated if the patient is breast-feeding or, of course, is pregnant again. Postpartum follow-up with appropriate assessment by a clinical endocrinologist should be continued until the patient is in a stable euthyroid state.

Euthyroid pregnant patients treated for Graves' disease before the pregnancy may still have stimulating thyroid autoantibodies in the circulation, which can cross the placenta. Measurement of maternal thyroid-stimulating immunoglobulins (TSI) thyrotropin receptor antibodies (TRAb) may be useful for assessment of potential fetal risk; on the basis of clinical judgment, the endocrinologist can have this study done.

Graves' Ophthalmopathy

Exophthalmos and other eye signs are the hallmark of Graves' disease and may occasionally be seen in the absence of hyperthyroidism. Severe Graves' ophthalmopathy occurs in a minority of patients with Graves' diathesis who are clinically euthyroid. The presence of ophthalmopathy requires a thorough thyroid evaluation. Orbital ultrasonography, computed tomography, or magnetic resonance imaging of the orbit may be necessary, particularly in cases of unilateral exophthalmos. The finding of characteristic extraocular muscle swelling helps exclude the presence of a retroorbital tumor. Serial exophthalmometry can document progression of the exophthalmos; such measurements are easily obtained during office visits. The rationale for local mechanical therapies--such as sunglasses, artificial tears, elevation of the head of the bed, bedtime diuretics, and use of eye protectors during sleep--should be explained to the patient in an effort to enhance adherence to recommendations. More aggressive treatment with corticosteroids, retroorbital irradiation, or surgical intervention can be considered for progressive and severe ophthalmopathy. Consultation with an ophthalmologist experienced in the treatment of orbital disease is recommended in the management of such cases.

In patients with established ophthalmopathy, a course of corticosteroid therapy begun at the same time as administration of Iodine 131 (^{131}I) decreases the possibility of worsening the ophthalmopathy. The potential side effects of corticosteroids should be considered in the decision about such preventive treatment.

Patients Taking Amiodarone

Amiodarone therapy causes thyroid dysfunction in 14 to 18% of the involved patients. Therefore, before initiation of such therapy, patients should have a baseline TSH measurement, and then they should be monitored at 6-month intervals during treatment. In patients receiving amiodarone, either hypothyroidism, which is treated with levothyroxine replacement, or hyperthyroidism may develop. Amiodarone-induced hyperthyroidism is of two types. Type 1 is similar to iodine-induced hyperthyroidism (jodbasedow phenomenon) and manifests with a low TSH level, a high free T_4 or T_3 estimate,

and a low radioiodine uptake. Doppler ultrasonography shows increased vascularity of thyroid tissue, similar to that in Graves´ disease. Because of low radioiodine uptake, Iodine 131 (^{131}I) treatment cannot be used, and use of antithyroid drugs has yielded only varied success. Although mild cases have resolved even when amiodarone therapy has been continued, consideration of ceasing this drug treatment is recommended. Restoration of euthyroidism may take months after cessation of amiodarone therapy. Type 2 amiodarone-induced hyperthyroidism resembles a destructive thyroiditis. Laboratory values and radioiodine uptake are similar to the findings in Type 1; however, Doppler ultrasonography shows decreased vascularity of the thyroid tissue. Corticosteroid treatment is recommended, and patients sometimes require surgical removal of the thyroid.

Subclinical Hyperthyroidism

Subclinical hyperthyroidism is characterized by a serum TSH level <0.1 microIU/mL and normal free T_4 and T_3 estimates. The low TSH levels result from either exogenous TSH suppression or endogenous production of thyroid hormones that, presumably, is sufficient to keep free T_4 and free T_3 levels normal but suppress pituitary TSH production and secretion. Most studies report a prevalence of < 2% in the adult or elderly population.

The clinical significance of subclinical hyperthyroidism relates to three risk factors: (a) progression to overt hyperthyroidism, (b) cardiac effects, and (c) skeletal effects. In patients who are receiving levothyroxine for replacement therapy, the dose should be adjusted so serum TSH values range from 0.3 to 3.0 microIU/mL. An exception is thyroid hormone replacement treatment after thyroidectomy for differentiated thyroid cancer, in which case a mildly to moderately suppressed TSH level is generally desirable. In addition, some physicians treat hypofunctional thyroid nodules with levothyroxine in doses sufficient for minimal suppression of the TSH level.

In patients with subclinical hyperthyroidism attributable to nodular thyroid disease, treatment seems warranted because of the high rate of conversion to clinical hyperthyroidism. Recent studies have suggested that prolonged subclinical hyperthyroidism may be associated with decreased bone mineral density. Accordingly, investigators have concluded that subclinical hyperthyroidism should be considered a risk factor for osteoporosis, particularly in postmenopausal women. In men and premenopausal women, bone loss seems to be minimal and of unknown clinical significance. In elderly patients with subclinical hyperthyroidism, the relative risk for atrial fibrillation increases threefold. Other adverse cardiac effects include impaired left ventricular diastolic filling and impaired ventricular ejection fraction response to exercise.

No consensus exists about the management of subclinical hyperthyroidism. One recent review of the topic suggested that, in most patients, treatment is unnecessary, but thyroid function tests should be performed every 6 months. The American Association of Clinical Endocrinologists (AACE) recommends that all patients with subclinical hyperthyroidism should undergo periodic clinical and laboratory assessment to determine individual therapeutic options.

Clearly, once a suppressed TSH level has been detected in a specific patient, a reassessment is appropriate to ensure that the suppressed TSH level is persistent rather than transient.

Therefore, the guideline authors' suggestion is to reassess the TSH level along with free T_4 and T_3 estimates in 2 to 4 months. If a sustained TSH suppression (< 0.1 microIU/mL) is established, then management should be based on an individual program. For example, patients with symptoms of hyperthyroidism, atrial fibrillation, or unexplained weight loss would be appropriate candidates for treatment. Women with osteopenia or osteoporosis should undergo assessment for treatment. In patients with multinodular goiter, treatment should be considered. The treatment options include antithyroid drugs or radioactive iodine. Obviously, in elderly women with osteoporosis, the treatment protocol should include calcium, estrogen, bisphosphonates, or some combination of these agents.

Hypothyroidism

Although most physicians can diagnose and treat hypothyroidism, in certain situations a clinical endocrinologist experienced in the spectrum of thyroid disease would be most likely to recognize the more subtle manifestations of hypothyroidism and most skilled in the physical examination of the thyroid gland (refer to original guideline document for details about differential diagnosis). Consultation with an endocrinologist is recommended in the following situations:

- Patients of age 18 years or less
- Patients unresponsive to therapy
- Pregnant patients
- Cardiac patients
- Presence of goiter, nodule, or other structural changes in the thyroid gland
- Presence of other endocrine disease

Not all patients with chronic thyroiditis have hypothyroidism, and if it is present, it may not persist. Rarely, patients with chronic thyroiditis have a change from a hypothyroid to a nonsuppressible euthyroid state or even to a hyperthyroid state because of the development of stimulating TSH receptor autoantibodies (TSI or TRAb) of Graves' disease. If such patients had been receiving levothyroxine treatment, downward dose adjustments or even cessation of levothyroxine therapy might be required. Therefore, adequate follow-up evaluations are imperative. The patient should be informed that this treatment adjustment may be necessary. When a patient has a goiter, a complete assessment, including a comprehensive history and physical examination and appropriate laboratory evaluation, should be performed. Patients with chronic thyroiditis have a high incidence of other associated autoimmune diseases such as vitiligo, rheumatoid arthritis, Addison's disease, diabetes mellitus, and pernicious anemia.

Diagnosis

Laboratory Evaluation

Appropriate laboratory evaluation is critical to establish the diagnosis and cause of hypothyroidism in the most cost-effective way. The most valuable test is a

sensitive measurement of TSH level. A TSH assay should always be used as the primary test to establish the diagnosis of primary hypothyroidism.

Additional tests may include the following:

- Free T_4 estimate
- Thyroid autoantibodies--anti-thyroid peroxidase and antithyroglobulin autoantibodies
- Thyroid scan, ultrasonography, or both (if necessary to evaluate suspicious structural thyroid abnormalities)

Refer to the original guideline document for information on differential diagnosis.

Treatment and Management

Chronic Thyroiditis/Subclinical Hypothyroidism/Clinical Hypothyroidism

The treatment and management of chronic thyroiditis and clinical hypothyroidism must be tailored to the individual patient. Many clinical endocrinologists treat the goiter of chronic thyroiditis with levothyroxine, even in patients with a normal level of TSH, and all physicians will treat clinical hypothyroidism with levothyroxine replacement therapy. The management of subclinical hypothyroidism is addressed in the subsequent section.

The American Association of Clinical Endocrinologists (AACE) advocates the use of a high-quality brand preparation of levothyroxine. Bioequivalence of levothyroxine preparations is based on total T_4 measurement and not TSH levels; therefore, bioequivalence is not the same as therapeutic equivalence. Furthermore, various brands of levothyroxine are not compared against a levothyroxine standard. Preferably, the patient should receive the same brand of levothyroxine throughout treatment. In general, desiccated thyroid hormone, combinations of thyroid hormones, or triiodothyronine should not be used as replacement therapy. The mean replacement dosage of levothyroxine is 1.6 micrograms/kg of body weight per day, although the appropriate dosage may vary among patients. The appropriate pace of treatment depends on the duration and severity of the hypothyroidism and on the presence of other associated medical disorders. The initial levothyroxine dosage may range from 12.5 micrograms daily to a full replacement dose based on the age, weight, and cardiac status of the patient and the severity and duration of the hypothyroidism. Importantly, patients should undergo reassessment and therapy should be titrated after an interval of at least 6 weeks following any change in levothyroxine brand or dose. The serum TSH level is most important, and a free T_4 estimate may be included in the assessment as well. Once the TSH level is in the normal range, the frequency of visits can be decreased. Although each patient´s care must be individualized, a follow-up visit in 6 months and then annually is a common schedule. During follow-up assessments, an appropriate interim history should be recorded, and physical examination should be performed in conjunction with pertinent laboratory tests. Involving the patient in the levothyroxine treatment by explaining the thyroid disease and potential consequences should result in improved adherence to recommendations.

Thyroid hormone absorption can be affected by malabsorptive states and patient age. In addition, commercially available levothyroxine products may not be bioequivalent. Because levothyroxine has a narrow therapeutic range, small differences in absorption can result in subclinical or clinical hypothyroidism or hyperthyroidism. Drug interactions also present a problem. Certain drugs, such as cholestyramine, ferrous sulfate, sucralfate, calcium, and some antacids containing aluminum hydroxide, interfere with levothyroxine absorption. Other drugs such as anticonvulsants affect thyroid hormone binding, whereas others such as rifampin and sertraline hydrochloride may accelerate levothyroxine metabolism and necessitate a higher replacement dose. The physician must make the appropriate adjustments in levothyroxine dosage in the face of absorption variability and drug interactions. Inappropriate levothyroxine replacement can result in increased costs because of the need for additional patient visits and laboratory tests.

Recent studies have shown a resurgence of interest in the possible benefits of treatment of hypothyroidism with combinations of T_4 and T_3 or with natural thyroid preparations. The small-scale study that seems to have sparked this interest treated patients for only 5 weeks, focused on mood changes, used a T_4 plus T_3 combination that differs substantially from that found in natural thyroid products, may have found benefit in only a subset of patients, and has not been replicated. Insufficient evidence is available to know which patients with hypothyroidism, if any, would be better treated with a combination of T_4 plus T_3 rather than with T_4 alone.

Subclinical Hypothyroidism

Subclinical hypothyroidism refers to mildly increased serum TSH levels in the setting of normal free T_4 and T_3 estimates. Although subclinical hypothyroidism may represent "early" thyroid failure, it may occur in the presence or absence of symptoms. It is a common disorder, the prevalence ranging from 1 to 10% of the adult population with increasing frequency in women, in patients with advanced age, and in those with greater dietary iodine intake. Usually, subclinical hypothyroidism is asymptomatic and is discovered on routine, screening TSH determination. The most common cause of subclinical hypothyroidism is autoimmune thyroiditis (Hashimoto's disease). Progression to overt hypothyroidism is reported to vary from 3 to 20%, the risks being greater in those patients with goiter or thyroid antibodies (or both).

Although subclinical hypothyroidism is often asymptomatic, potential risks associated with the condition include progression to overt hypothyroidism, cardiovascular effects, hyperlipidemia, and neuropsychiatric effects. Recent studies have suggested that treatment of subclinical hypothyroidism will reduce cardiovascular risk factors, improve the lipid profile, and minimize neurobehavioral abnormalities. Some of these data, however, were derived from studies that included patients with TSH levels well above 10 microIU/mL; for patients with mildly increased TSH levels (5 to 10 microIU/mL), the data are controversial.

Treatment of subclinical hypothyroidism remains controversial, and recent arguments for and against treatment have been proposed. The guideline authors believe that treatment is indicated in patients with TSH levels >10 microIU/mL or in patients with TSH levels between 5 and 10 microIU/mL in conjunction with

goiter or positive anti-thyroid peroxidase antibodies (or both). These patients have the highest rates of progression to overt hypothyroidism. An initial dosage of levothyroxine of 25 to 50 micrograms per day can be used, the serum TSH level should be measured in 6 to 8 weeks, and the levothyroxine dose should be adjusted as necessary. The target TSH level should be between 0.3 and 3.0 microIU/mL. Once a stable TSH level is achieved, annual examination is appropriate.

Hypothyroidism during Pregnancy

Untreated overt hypothyroidism during pregnancy may increase the incidence of maternal hypertension, preeclampsia, anemia, postpartum hemorrhage, cardiac ventricular dysfunction, spontaneous abortion, fetal death or stillbirth, low birth weight, and, possibly, abnormal brain development. Evidence from a population-based study suggests that even mild, asymptomatic, untreated maternal hypothyroidism during pregnancy may have an adverse effect on cognitive function of the offspring and that this outcome can be prevented by thyroid hormone replacement therapy. Mildly increased serum TSH levels during pregnancy might also increase the risk of fetal death, but whether treatment prevents this complication is not yet known. In most of these women, thyroid antibodies develop--a finding that seems to be a risk factor for spontaneous abortion independent of thyroid hormone and TSH levels. Because levothyroxine therapy is safe during pregnancy, thyroid hormone replacement treatment seems advisable for all pregnant women with hypothyroidism, even if it is mild. As a further recommendation, TSH measurement should be routine before pregnancy or during first trimester screening for thyroid dysfunction.

When a woman with hypothyroidism or underlying chronic thyroiditis becomes pregnant, the thyroid function may change; it can improve in some mild cases or deteriorate in others. In general, the dosage of thyroid hormone should be increased in patients with moderate to severe hypothyroidism. These patients should undergo assessment of their serum TSH level every 6 weeks during pregnancy to ensure that the requirement for levothyroxine has not changed.

Hypothyroidism and Concurrent Conditions

Diabetes Mellitus

In approximately 10% of patients with type 1 diabetes mellitus, chronic thyroiditis will develop during their lifetime, which may include the insidious onset of subclinical hypothyroidism. Of importance, patients with diabetes should be examined for the development of a goiter. Sensitive TSH measurements should be obtained at regular intervals in patients with diabetes, especially if a goiter develops or if evidence is found of other autoimmune disorders. In addition, postpartum thyroiditis will develop in up to 25% of women with type 1 diabetes.

Infertility

Some patients with infertility and menstrual irregularities have underlying chronic thyroiditis in conjunction with subclinical or clinical hypothyroidism. Typically, these patients seek medical attention because of infertility or a previous miscarriage, rather than hypothyroidism. Chronic thyroiditis can be identified by a

careful, comprehensive history, physical examination, and appropriate laboratory evaluation. In some patients with elevated TSH levels, levothyroxine replacement therapy may normalize the menstrual cycle and restore normal fertility.

Depression

The diagnosis of subclinical or clinical hypothyroidism must be considered in every patient with depression. In fact, a small proportion of all patients who are depressed have primary hypothyroidism--either overt or subclinical. Moreover, all patients on lithium therapy need periodic thyroid evaluation because lithium may induce goiter and hypothyroidism.

The diagnosis of chronic thyroiditis or subclinical or clinical hypothyroidism is based on a high serum TSH level and positive thyroid autoantibodies. Appropriate levothyroxine replacement therapy should be instituted. Occasionally in psychiatric practice, some patients who have depression are treated not only with antidepressants but also with thyroid hormone replacement, even though they have normal thyroid function. No firm evidence has shown that thyroid hormone treatment alone does anything to alleviate depression in such individuals.

Euthyroid Sick Syndrome

The evaluation of thyroid function in chronically ill patients may be confusing. Many medications, such as corticosteroids and dopamine, may interfere with the results of thyroid function tests. In addition, when a patient is ill or starving, the body tends to compensate by decreasing metabolic rates, which may result in a low free T_4 or T_3 estimate and a normal or low TSH level. If the TSH value is less than 10 microIU/mL, treatment should ideally be deferred until the patient´s medical condition has resolved. Assessment of the patient by a clinical endocrinologist is appropriate before initiation of levothyroxine treatment.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Improved physician education about overt and subclinical hyperthyroidism and hypothyroidism
- Decreased morbidity due to either overt or subclinical hyperthyroidism and hypothyroidism

POTENTIAL HARMS

Complications Associated with Treatments for Hyperthyroidism

- Surgical intervention--complications include hypoparathyroidism and vocal cord paralysis in a small proportion of patients
- Antithyroid drug treatment--risks include adverse reactions such as minor skin rashes and, in rare instances, agranulocytosis and hepatitis
- Radioactive iodine--most patients become hypothyroid and require lifelong thyroid replacement therapy. Patients must adhere to precautions after radioactive iodine treatment to avoid contaminating others, especially infants and young children. Sore throat or neck pain may also develop after treatment.
- The potential side effects of corticosteroids should be considered in the decision about such preventive treatment for ophthalmopathy.

Complications Associated with Thyroid Hormone Treatment for Hypothyroidism

Overreplacement may be associated with the following:

- Accelerated bone loss leading to increased bone fractures
- Cardiac consequences including atrial fibrillation and cardiac hypertrophy

Inappropriate levothyroxine replacement in patients with hypothyroidism can result in increased costs because of the need for additional patient visits and laboratory tests. Adjustments of levothyroxine dosage may be necessary due to adsorption variability and drug interactions.

Subgroups Most Likely to be Harmed:

- Radioactive iodine therapy should be deferred in women who are breast-feeding because it appears in the breast milk.
- Postmenopausal women are at particular risk of accelerated bone loss leading to increased bone fracture as a result of overreplacement of thyroid hormone.

CONTRAINDICATIONS

CONTRAINDICATIONS

Radioactive iodine is contraindicated during pregnancy because it may ablate the thyroid in the fetus

QUALIFYING STATEMENTS

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- These guidelines established by the American Association of Clinical Endocrinologists (AACE) present several approaches to the assessment and treatment of patients with hyperthyroidism and hypothyroidism. They

highlight the complexity of thyroid diseases and describe diagnostic and therapeutic strategies in various settings. These guidelines are not intended to be a comprehensive outline of therapeutic options.
- Subclinical thyroid disease often remains undiagnosed. Through sound judgment, timely intervention, initiation of appropriate treatment, and patient involvement, an optimal level of care is attainable.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

AACE Thyroid Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocr Pract 2002 Nov-Dec;8(6):457-69. [46 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1996 (revised 2002)

GUIDELINE DEVELOPER(S)

American Association of Clinical Endocrinologists - Medical Specialty Society
American College of Endocrinology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Association of Clinical Endocrinologists (AACE)

GUIDELINE COMMITTEE

American Association of Clinical Endocrinologists (AACE) Thyroid Task Force

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Task Force Members: H. Jack Baskin, MD, FACE, Chairman; Rhoda H. Cobin, MD, FACE; Daniel S. Duick, MD, FACE; Hossein Gharib, MD, FACE; Richard B. Guttler, MD, FACE; Michael M. Kaplan, MD, FACE; Robert L. Segal, MD, FACE

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of this guideline.

It updates a previous version: American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE). AACE clinical practice guidelines for the evaluation and treatment of hyperthyroidism and hypothyroidism. Jacksonville (FL): AACE; 1996. 24 p. (AACE clinical guidelines; no. 1996).

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American Association of Clinical Endocrinologists (AACE) Web site.

Print copies: Available from American Association of Clinical Endocrinologists, 1000 Riverside Ave., Suite 205, Jacksonville, FL 32204.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on October 1, 1998. The information was verified by the guideline developer on December 15, 1998. This summary was updated by ECRI on February 27, 2003. The information was verified by the guideline developer on March 24, 2003.

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